MANAGEMENT OF THE PATIENT WITH COR PULMONALE*

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COR pulmonale is here defined as heart disease caused by disorders of the lungs, the pulmonary vessels, or the ventilatory apparatus. Such disorders cause heart disease principally by causing pulmonary hypertension although severe hypoxia, which is often present, may also have an adverse effect on the myocardium. Pulmonary hypertension is usually caused either by widespread obliteration of the vascular bed or by chronic alveolar hypoventilation.[1] In obliterative disease hypertension is relatively fixed. In hypoventilatory disease it is potentially reversible.[2] When vascular obliteration and hypoventilation are both present in a particular case it is generally clear which is the dominant process. The nature of the treatment and the results to be expected depend greatly on whether obliterative or hypoventilatory disease is principally responsible for cor pulmonale. For this reason, a brief illustrative classification of disorders commonly responsible for cor pulmonale will be presented first, based on this primary distinction, after which the treatment of obliterative and hypoventilatory cor pulmonale will be discussed separately.

AN ETIOLOGICAL CLASSIFICATION OF COR PULMONALE

1) *Disorders Causing Pulmonary Vascular Obliteration:*

   a) *Diffuse pulmonary fibrosis:* sarcoidosis,[3] pneumoconioses such as berylliosis, asbestosis, and silicosis,[4] disorders of unknown cause (Hamman-Rich syndrome).[5]

   b) *Obstructive vascular disease:* recurrent pulmonary embolism,[6]

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primary pulmonary hypertension,[7] schistosomiasis,[8] collagen disorders.[9]

2) *Disorders Causing Alveolar Hypoventilation:*

a) *Diminished sensitivity of the respiratory center.*[10]

b) *Disorders of the chest bellows:* neuromuscular disease such as poliomyelitis,[11] chest deformity,[12] especially kyphoscoliosis, extreme obesity.[13]

c) *Chronic broncho-obstructive disease.*[14]

Certain combinations of these factors may cause cor pulmonale, such as diffuse, chronic pulmonary tuberculosis with thoracoplasty and advanced silicosis with emphysema. In many cases of cor pulmonale associated with broncho-obstructive disease actual loss of part of the pulmonary vascular bed must contribute to the severity of pulmonary hypertension even though most of the pressure elevation depends on hypoventilation.

The recognition of hypoventilation as a factor of primary importance in causing cor pulmonale, and the demonstration that the pulmonary hypertension and circulatory failure of these patients are reversible if hypoventilation can be controlled, were fundamental contributions of the greatest significance to this field.[15, 16] These basic discoveries and their subsequent elaboration have provided the rational foundation for most of the effective present-day treatment of hypoventilatory cor pulmonale. It is now well established that alveolar hypoxia[17-19] can cause pulmonary hypertension, and evidence is mounting that hypercapnia and acidosis[20-22] also contribute.

In obliterative disease, pulmonary hypertension is not in general reversible, so that therapeutic opportunities are more limited than in hypoventilatory disease. However, in some cases of obliterative disease, such as primary pulmonary hypertension, there is evidence that a significant degree of pulmonary vasoconstriction exists.[23] In planning the treatment of cor pulmonale it is fundamental to distinguish between obliterative and hypoventilatory disease. This is done most directly by measurement of the arterial blood CO_2 tension. In obliterative disease this is characteristically normal or low. In hypoventilatory cor pulmonale it is usually above 60 mm. Hg.[14] When metabolic alkalosis can be excluded, an elevation of the serum CO_2 combining capacity to 35 mEq. per liter or more indicates that significant hypoventilation is present.

Treatment of Cor Pulmonale Caused by Pulmonary Vascular Obliteration

Once obliterative cor pulmonale is established, little can be offered in most cases beyond the conventional treatment of congestive heart failure by digitalization, diuretics, and restriction of activity. The latter is particularly important because of the sharp rise in pulmonary arterial pressure associated in these patients with an increase in cardiac output. Venesection is occasionally desirable to prevent hematocrit elevations above 55 per cent. When failure is present, oxygen should be used to relieve arterial oxygen unsaturation, insofar as this may be possible. While carbon dioxide narcosis is not a problem in these patients, it should be remembered that undiluted oxygen can produce tracheobronchial irritation and even pneumonitis when used unremittingly for many hours.[24] Fifty per cent oxygen can be given almost indefinitely without apparent damage.[25] Several drugs have been found to reduce elevated pulmonary vascular[26-32] resistance of different causes in man. None of these has yet proved to be generally helpful in obliterative cor pulmonale in spite of the evidence that pulmonary vascular resistance may be transiently reduced by drugs even in some of these cases. With the development of radioisotopic[33] and angiographic[34] techniques for detecting and localizing pulmonary embolic disease, direct surgical approaches to the relief of embolic pulmonary arterial obstruction are beginning to be made.[35]

The difficulties of treatment emphasize the importance of preventive measures. Pulmonary sarcoidosis and other conditions that lead to diffuse pulmonary fibrosis may occasionally be checked by appropriate steroid therapy before extensive scarring has occurred.[36, 37] When chronic embolic disease is recognized early enough, the use of anticoagulants, caval litigation, and other procedures may avert the development of cor pulmonale.[38] The prevention of pneumoconioses is of obvious importance.

Treatment of Cor Pulmonale Caused by Hypoventilatory Disorders

The aim in managing hypoventilatory cor pulmonale is primarily to maintain adequate alveolar ventilation. Management includes measures intended to prevent, retard, or improve the basic disorders respon-

sible for chronic hypoventilation; to prevent heart failure by maintaining adequate alveolar ventilation despite the handicap imposed by the basic disorder; and to treat established cardiorespiratory failure by a combination of conventional means and special measures designed to restore adequate ventilation.

It is apparent that prevention or treatment of the basic disorders responsible for chronic hypoventilation will vary according to the specific disorder. However, the approaches to maintaining adequate alveolar ventilation and the treatment of established cardiorespiratory failure in broncho-obstructive disease also apply in large part to other hypoventilatory disorders. Consequently, the discussion of therapy in hypoventilatory cor pulmonale will be directed toward broncho-obstructive disease but with references to other disorders where appropriate.

Prevention of Failure by Maintaining Ventilation in Broncho-Obstructive Disease

Maintaining a clear airway and a strong, mobile chest bellows system are the basic considerations.

Every effort should be made to minimize bronchitis. Smoking must be strictly forbidden. Cigarette smoking is the most important identifiable factor in the production of chronic bronchitis in this country.[39] The physician's attitude on this point should be forceful and unequivocal. At the same time he should be patient and persistent. Many persons who eventually abandon smoking completely have one or more lapses on the way. Such lapses characteristically occur in times of tension or loss. The substitution of a pipe or cigars is useless in the treatment of bronchitis because converted cigarette smokers continue to inhale. Irritating industrial fumes, smog, or dusty environments should be avoided.

Exposure to respiratory infections should be minimized by avoiding public conveyances and crowds as much as possible during the winter months. Polyvalent influenza vaccine should be given annually. The use of continuous prophylactic antibiotic therapy during the months of greatest risk from respiratory infections has been reported to be effective.[40-42] Some patients apparently benefit from the prolonged use of a broad-spectrum antibiotic such as tetracycline, 250 mg. four times a day. In most cases it is satisfactory to treat respiratory infections promptly but to discontinue antibiotics after the sputum becomes non-

purulent. In so doing the physician recognizes that he is often treating an infection of viral origin, but the effect on secondary bacterial invaders may still be helpful. The pathogenic bacteria most frequently isolated from the sputum in patients with bronchitis are *Hemophilus influenzae*, *pneumococci*, *staphylococci*, and Gram-negative organisms, especially Klebsiella.[41-43] In the treatment of frank pneumonia it is useful to remember that *Mycoplasma pneumoniae*, the etiologic agent in primary atypical pneumonia, is responsive to tetracycline.

Most patients with broncho-obstructive disease benefit from regular postural drainage for 5 to 20 minutes two or three times a day. This should be preceded by the use of a nebulized bronchodilator. The techniques of postural drainage are conveniently illustrated for patients in a recent booklet.[44]

Breathing exercises have been useful to many patients with broncho-obstructive disease.[45, 46] The techniques of these have been well described. Their satisfactory employment demands repeated instruction and coaching by a physiotherapist and an attitude of interest and enthusiasm on the part of the physician. While the primary object of most breathing exercises is to provide training in diaphragmatic and abdominal breathing, they serve other purposes as well. These include the maintenance of mobility in the costovertebral joints, improvement in strength of all the respiratory muscles, and the emphasis on prolonged, unhurried expiration as the most effective way of achieving a good tidal volume. Barach[47, 48] and Miller and his associates[49] have also emphasized the advantages of general muscular conditioning. Remarkable rehabilitation has been achieved in some of these patients by carefully supervised exercise. In patients with severe ventilatory limitation the performance of this exercise is facilitated by inhalation of oxygen. This prevents the marked drop in arterial oxygen saturation that these patients frequently exhibit during exertion.

Nebulized bronchodilators are quite helpful in patients with chronic bronchitis and numerous preparations are available. They should be used on a regular schedule, and in patients who have active bronchial disease, a minimum of four treatments of 0.2 to 1.0 ml. 1:200 Isoproterenol per day is usually necessary to maintain adequate bronchial drainage.[43] Mucolytic agents are often added. Those times generally most effective and beneficial to the patient are: 1) first thing upon awakening, before arising, 2) before lunch, 3) before dinner, and 4) at

bedtime. During more severe exacerbation of symptoms, these treatments may need to be increased to as often as every two hours. The dosage and frequency of treatment must be tailored to the patients' needs.[43] The technique by which bronchodilator aerosols are administered is important to their efficacy. Inhalation of the aerosol should be preceded by a prolonged, slow expiration, the purpose of which is to empty partially those regions of the lung that are being poorly ventilated. Since these have been shown to fill early in the course of the subsequent inspiration, the oropharynx should already be full of aerosol when inspiration begins. The inspiration itself ought to be relatively slow, since this will provide a more even distribution of the aerosol than will a rapid inspiration. A rapid inspiration delivers the medication primarily to those airways that are already most widely open. Excessive use of bronchodilators causes undesirable tachycardia.

Intermittent positive pressure breathing (IPPB) devices have been widely used in the treatment of hypoventilatory disorders. They provide a convenient means of administering bronchodilator and mucolytic agents. The introduction of heated containers (125° F.) for nebulization of water into the mainstream output offers a most effective means of wetting the tracheobronchial tree and mobilizing viscid secretions.[50, 51] The containers can be kept free of Gram-negative bacteria by nebulizing a solution of 0.25 per cent acetic acid for 5 minutes each day.[52] IPPB for 20 minutes three or four times a day, or even for longer periods, has been widely used as a regular routine in the treatment of broncho-obstructive disease. One study has indicated that such a routine often causes an improvement in the arterial blood gases that is sustained in the interval between treatments.[53] It appears probable that the use of IPPB in this fashion may benefit patients with hypoventilatory disease of various causes by helping to maintain the mobility and compliance of the thoracic cage. In patients with severe impairment of the respiratory muscles, such as may be caused by poliomyelitis, compliance of the thoracic cage may decrease markedly if proper measures are not taken to maintain normal mobility. The decrease in compliance can cause a respiratory insufficiency that is reversible when the chest wall is remobilized by repeated use of a respirator, at a large tidal volume. It is probable that the same sequence of events may occur in other disorders where respiratory excursions are limited.

Corticosteroids have been overused in treating broncho-obstructive

disease, but occasionally they may be beneficial. As described later, they are probably helpful, together with antibiotics, in treating respiratory insufficiency precipitated by acute bronchitis. Some patients with chronic bronchitis who have unusually high airway resistance, apparently due to inflamed, thickened mucosa and increased tone of the bronchial musculature, can be markedly improved by relatively small doses of corticosteroids when other efforts have been unsuccessful. It may be necessary to start with larger than usual doses with reduction as rapidly as feasible to a maintenance level. The long-term use of low doses of steroids, such as 10 mg. of Prednisone every other day, appears to be justified when the patient can not be comfortable without steroids in spite of scrupulous attention to other therapeutic measures.

The physician who is following a patient with hypoventilatory disease should be alert for the early signs of cardiorespiratory insufficiency. The most direct evidence of developing insufficiency is an increase in the arterial blood carbon dioxide tension (pCO_2) and a decline in the oxygen tension (pO_2). Increase in the serum CO_2 combining capacity and in the hematocrit are usually reliable indicators. It should be remembered, however, that metabolic alkalosis induced by diuretics and steroids will also increase the CO_2 combining capacity. Serial determinations of ventilatory function, such as the vital capacity or the forced expiratory volume, can provide valuable objective evidence of progressive deterioration. Evidences of increased extracellular fluid volume make their appearance at a later stage. These include unexpected weight gain, ankle edema, increase in venous pressure, hepatomegaly, and widening of the cardiac silhouette by roentgenogram. While conventional treatment for congestive failure is appropriate at this stage, it is much more important to improve alveolar ventilation, since defective ventilation is responsible for the failure.

The occurrence of cardiorespiratory insufficiency in patients with broncho-obstructive disease may depend on causes other than progression of bronchitis and emphysema. Among these are spontaneous pneumothorax, the development of large cysts that compress the surrounding lung, emotional depression, and the occurrence of unrelated lung disease. Bronchogenic carcinoma is not uncommon in these elderly cigarette smokers. Patients with broncho-obstructive disease do not ordinarily have clubbing of the digits, and the appearance of this sign should stimulate a search for other pathology.

When heart failure appears in a patient with broncho-obstructive disease, there may be uncertainty whether failure is owing to hypoventilation or to some other cause. The decision is occasionally difficult, but hypoventilatory heart failure has some characteristics that can help differential diagnosis. When heart failure is caused by hypoventilation, the arterial pCO_2 is usually greater than 60 mm. Hg, and the arterial oxygen saturation less than 80 per cent.[14] As pointed out by Ebert,[54] the apex impulse is not felt in the left chest because the heart is vertical and the apex is covered by the distended lung. The cardiac impulse is felt readily in the subxiphoid region. Pleural fluid is very unusual. Arrhythmias used to be considered unusual in all varieties of chronic cor pulmonale, but transient arrhythmias often occur.[55] Many patients with broncho-obstructive disease and cor pulmonale also have additional disease of a different variety and it may be impossible to ascribe failure to a single cause.

The Treatment of Established Hypoventilatory Failure

The primary object of treatment is to improve the aeration of the blood. In hypoventilatory disorders oxygenation of the blood is readily improved by administering oxygen, but it is necessary to increase alveolar ventilation in order to improve elimination of carbon dioxide.

Oxygen must be administered to these severely hypoxic patients. In some persons with hypoventilatory failure the use of oxygen reduces ventilation by removing the respiratory stimulus of hypoxia.[56] Respiratory depression by oxygen may be severe enough to allow accumulation of carbon dioxide to the extent of producing carbon dioxide narcosis.[57] The danger can be avoided by giving oxygen at a rate slow enough to diminish hypoxia markedly but not to return the arterial oxygen tension entirely to normal levels. This can be done by administering oxygen through a nasal catheter at a rate of 1 l. a minute, by use of an oxygen tent at 4 to 6 l. per minute, or by IPPB at 30 to 40 per cent oxygen.

Ventilation is increased by clearing the airways, stimulating the patient's own ventilatory effort, and by using a respirator if necessary. For the proper management of these patients it is essential to have the guidance of repeated arterial blood gas measurements. Sedation should be avoided. Even without sedation many patients with hypoventilation become worse after admission to the hospital. When the hospitalized

patient is put comfortably at bed rest and relieved of the need to care for himself he loses much of the neurogenic stimulus to breathing that he had in his home situation. For this reason it is often advisable to keep newly hospitalized patients with hypoventilation in a reclining chair rather than in bed, when hospital facilities permit. The frequent use of IPPB helps maintain a satisfactory state of arousal. When IPPB is given on a regular schedule, it also provides automatically for inspection of the patient's responsiveness by the attendant administering the therapy. Caffeine in doses of 150 to 250 mg. orally or parenterally may help to sustain the patient's ventilatory effort. Ethamivan by the intravenous route is a more potent respiratory stimulant[58-60] but its use requires careful regulation of the rate of administration, and opinion is divided as to over-all benefit from the drug.[61, 62]

Antibiotics are used for the control of bronchitis, since this is the factor most commonly responsible for precipitating cardiorespiratory failure. The usual bacterial pathogens found in these patients have been described above. A combination of procaine penicillin, 600,000 units intramuscularly twice a day, and streptomycin 1 g. intramuscularly once or twice a day is often used. Tetracycline, 500 mg. orally 4 times a day, is often satisfactory. Other broad spectrum antibiotics or combinations of antibiotics may be used, depending on the results of cultures and of sensitivity determinations. Klebsiella may offer particular difficulty in treatment.[63] Corticosteroids may be used concomitantly with antibiotics for several days for the purpose of reducing inflammatory swelling of the bronchial mucosa and relaxing bronchospasm where this exists. Doses are in the range of 100 to 200 mg. of hydrocortisone or its equivalent.

The bronchial tree must be cleared of sputum as well as possible. Sputum is often viscid or inspissated. Bronchodilators can be used as described earlier. Intravenous aminophyllin may be helpful in relaxing bronchospasm. It can be administered conveniently by adding 500 mg. to a liter of 5 per cent dextrose in water. Heated water nebulization by IPPB is an effective means of wetting the bronchi. The most effective type of heated nebulizer is the main-stream nebulizer, so called because the flow of air under positive pressure from the positive-pressure apparatus passes through the nebulizer reservoir rather than nebulizing the mist from a side-arm nebulizer into the main-stream. We now routinely use a main-stream heated nebulizer attached directly to the

apparatus for the administration of IPPB to patients. The heater keeps the reservoir solution at 125° F. and the resulting supersaturated inspired air allows moisture to be deposited in the airway rather then contributing to further drying of the airway. This treatment is often given for 10 to 15 minutes every 1 to 2 hours. In some cases, patients may be given humidified aerosol almost continuously at atmospheric pressure using an oxygen supply or a small compressor to produce the aerosolization in the nebulizer. Distilled water, normal saline, or one of the surface-active agents, which may be most effective,[43] can be used in the heated nebulizer. If these measures are sufficient to obtain progressive improvement, as judged most reliably by arterial blood gas determinations, no more vigorous treatment may be needed. When the arterial CO_2 tension remains high despite these measures, a tracheostomy is usually required. It should be preceded, if possible, by bronchoscopic aspiration of the airways. This will remove collections of inspissated sputum that may be difficult to detect and clear by other means. In very lethargic or comatose patients with hypoventilatory failure, bronchoscopy and tracheostomy should be done at once. A tracheostomy has the incidental advantage of reducing respiratory dead space, but its main purpose is to permit frequent suctioning of the tracheobronchial tree. This should be done every 20 minutes for the first few hours, with care taken to enter both main-stem bronchi. Manipulation is facilitated by using a catheter with a curved tip. When alveolar ventilation is still inadequate after these measures, a respirator should be employed.

When a respirator is to be used, the patient should be sedated without hesitation if this is necessary to prevent his fighting the respirator. Most of the commonly available positive pressure respirators are suitable. Pressure-cycled respirators may be used through a tracheostomy equipped with a cuffed tube. These tubes must be replaced at least every 12 hours to avoid tracheal ulceration. Positive cycling pressures of about 20 cm. H_2O usually provide adequate ventilation. It is inadvisable to exceed 35 cm. of H_2O because of the possibility of damaging the lung. Negative pressure is ineffective. It is desirable to use a respirator that allows slowing the inflow rate down to levels as low as 15 or 20 l. per minute. At fast inflow rates the inordinately high airway resistance of these patients will cause the pressure to mount rapidly above the cycling point, and the tidal volume will be ineffective. Piston respirators, which are volume-cycled and safety-valved to prevent

developing high pressures, provide very effective ventilation for these patients. The available stroke volume is usually large enough to deliver an adequate tidal volume without inflating the cuff of the tracheostomy tube. The excess gas simply vents through the patient's upper airway. If this loss is excessive, it may be controlled by applying a respiratory mask over the mouth and nose. Tank respirators are also effective.

The use of a positive pressure or tank respirator tends to impede venous return and can readily produce dangerous hypotension in a hypercapnic patient. This is usually controlled without difficulty by pressor amines. When a respirator and pressor amines are required for many hours, the hematocrit should be followed to ensure that a decline in blood volume through hemoconcentration is not responsible for the difficulty in maintaining blood pressure.

Digitalis should be used in these patients because of the demonstration that this can increase the cardiac output and reduce the right ventricular end-diastolic pressure.[15] These patients are often overdigitalized.[64] Their heart rate is characteristically rapid, and this may induce the physician to overestimate the digitalis requirement. Hypokalemia is commonly present. The serum potassium may be reduced still further when respiratory acidosis is corrected by therapy, and this may precipitate digitalis intoxication. Thiazide diuretics or mercurials are employed in the usual doses. Acetazolamide, 500 mg. a day, is an effective diuretic while the serum bicarbonate is elevated.

With the use of a respirator frequent blood gas and electrolyte determinations are necessary. This is not only to ensure that the respirator is working as well as it should, but also to make certain that it is not overworking to the extent of producing an undesirable alkalosis. It has been pointed out that patients with hypoventilatory failure may present a picture of metabolic alkalosis.[65-67] This commonly develops during vigorous treatment.[68] Even without medication some patients may become potassium-deficient during the course of prolonged ventilatory insufficiency.[64] With the use of diuretics and corticosteroids potassium depletion is quite common in these patients. As part of the compensation for respiratory acidosis they retain bicarbonate and become chloride-depleted.[69-71] When the arterial pCO_2 is abruptly lowered toward normal by a modern piston respirator, marked alkalosis will develop. Cardiac arrhythmias may appear at this time, and may cause death.[66] Acute alkalosis can easily be avoided by monitoring the

blood gases and adjusting the respirator appropriately. The potassium deficit should be replaced. Schwartz and his associates have demonstrated the need to replace chloride in treating metabolic alkalosis in these patients.[72-74] The replacement of potassium and chloride may be started in patients on the respirator by adding 40 mEq./l. of KCl to 5 per cent dextrose in water given intravenously. During the early period of adjusting the respirator and the KCl infusion, these patients may advantageously be followed with an ECG monitor.

It should be emphasized strongly that these heroic measures can be avoided in most instances by good medical management and by intelligent, conscientious cooperation on the part of the patient.

Some Obvious Needs

It is evident that the management of cor pulmonale is a difficult matter. A significant amount of benefit can be derived by the application of presently known means. Improvement in the understanding, prevention, and timely treatment of the disorders that can destroy the pulmonary vascular bed and produce chronic hypoventilation is of course a fundamental need. The management of established disease would benefit greatly by the development of more effective anticoagulant or fibrinolytic agents; by the introduction of agents effective against respiratory viruses; and by the discovery of pharmacologic agents that are clinically effective in the reduction of pathologically increased pulmonary vascular tone. The striking effects on pulmonary vascular resistance that can be obtained by drugs under special circumstances suggest the possibility and the desirability of finding therapeutically useful pulmonary vasodilators.

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